An Attention Modulated Response to Disgust in Human Ventral Anterior Insula

Pierre Krolak-Salmon, MD,[1,2] Marie-Anna Hénaff, PhD,[2] Jean Isnard, MD,[1] Catherine Tallon-Baudry, PhD,[2] Marc Guénot, MD,[1] Alain Vighetto, MD, PhD,[1] Olivier Bertrand, PhD,[2] and François Mauguière, MD, PhD[1]

The human brain is expert in analyzing rapidly and precisely facial features, especially emotional expressions representing a powerful communication vector. The involvement of insula in disgust recognition has been reported in behavioral and functional imaging studies. However, we do not know whether specific insular fields are involved in disgust processing nor what the processing time course is. Using depth electrodes implanted during presurgical evaluation of patients with drug-refractory temporal lobe epilepsy, we recorded intracerebral event-related potentials to human facial emotional expressions, that is, fear, disgust, happiness, surprise, and neutral expression. We studied evoked responses in 13 patients with insular contacts to specify the insular fields involved in disgust processing and assess the timing of their activation. We showed that specific potentials to disgust beginning 300 milliseconds after stimulus onset and lasting 200 milliseconds were evoked in the ventral anterior insula in four patients. The occurrence and latency of event-related potentials to disgust in the ventral anterior insula were affected by selective attention. The analysis of spatial and temporal characteristics of insular responses to disgust facial expression lead us to underline the crucial role of ventral anterior insula in the categorization of facial emotional expressions, particularly the disgust.

In a recent review of the neuropsychology of emotions, Calder and colleagues addressed the question whether the different types of emotions are all coded by a single integrated system or individually processed by multiple and specific encoding systems.[1] One conclusion supported by numerous clinical and functional imaging studies is that neural mechanisms underlying emotions such as fear and disgust are separated, at least partly. Indeed, bilateral amygdala damage in humans affects recognition of fear from facial expressions[2]; degenerative and vascular lesions of insula and putamen impair recognition of disgust facial expression.[3,4] Thus, these brain structures appear to be essential in the processing of specific facial expressions. However, insular lesions studies do not allow a precise spatial approach of the insular fields involved in disgust processing. Neuroimaging studies pointed out the role of the anterior part of the insula in disgust recognition.[5,6] Primate insula has been divided in different cytoarchitectonic fields, each of them showing a specific neural connectivity,[7] but we do not know if disgust processing is performed by a specific insular field and its connected cortical areas. Moreover, the literature on human emotions brings very little information on the temporal processing of emotion recognition. In a previous study, using scalp event-related potentials (ERPs) to investigate facial emotions processing,[8] we observed latency differences according to the different facial expressions in the right temporal area. However, scalp ERPs do not allow us to draw any conclusions regarding the involvement of deep structures such as insula or amygdala. Intracranial recordings combine accurate spatial and temporal resolutions and are particularly appropriate to explore deep cerebral structures.[9,10] In this study, we recorded ERPs to different facial expressions, including disgust, in numerous sites of human insula using intracerebral electrodes during presurgical evaluation of patients with temporal lobe epilepsy (TLE). We looked for a possible effect of attention to facial expressions on evoked responses in this structure.

Patients and Methods

Patients

Patients suffering from drug refractory TLE were stereotactically implanted with depth electrodes for a presurgical eval-

uation. The structures to be explored were defined on the basis of ictal manifestations, electroencephalogram (EEG), and neuroimaging studies.[11] Among other sites, these patients had electrodes chronically implanted in the operculo-insular cortex for the recording of their seizures and cortical functional mapping using evoked potential recordings. Thirteen patients were included in this study: electrodes were implanted in the right insula for 10 and in the left insula for 3. This provided 17 insular electrode contacts with nonarte-facted EEG. The recording of visual-evoked potentials is part of the functional mapping of eloquent cortical areas performed routinely before epilepsy surgery in patients with depth electrodes implanted in temporooccipital cortex. According to the French regulations concerning invasive investigations with a direct individual benefit, patients were fully informed of the electrode implantation and stereotactic EEG and ERP recordings (SEEG) and gave their consent. At the time of ERP recordings, patients were under antiepileptic monotherapy. ERP recordings were performed at the end of the SEEG monitoring, once pertinent seizures had been recorded. Ten patients were right handed and three were left handed as determined by Edinburgh Handedness Inventory.

Surgical and Electrode Site Location

A cerebral angiography is first performed in stereotactic conditions. To reach the clinically relevant target, we calculated the stereotactic coordinates[12] of each electrode preoperatively on the individual cerebral magnetic resonance imaging (MRI) previously enlarged at the angiography scale. The electrodes were implanted perpendicularly to the midsagittal plane using Talairach's stereotactic grid.[13] Depth probes were 0.8mm in diameter and had 5, 10, or 15 recording electrode contacts. Contacts were 2.0mm long, and successive contacts were separated by 1.5mm. The accuracy of the registration procedure was approximately 2mm, estimated from another patient's MRI obtained just after electrode explantation.

Among the 13 patients included in the study, eight were also implanted in the fusiform or lingual gyri.

Stimuli and Experimental Paradigm

Stimuli were 40 static gray scale images of emotionally expressive faces (four women and four men referred to as E.M. J.J., P.E., W.F., C., M.F., P.F., and S.W., depicting five different emotional expressions, ie, fear, happiness, disgust, surprise, and neutral), taken from Ekman's set of pictures of facial affect.[14] The digitized, size-, brightness-, and contrast-adjusted images were presented on a computer screen 1.10 m from the subject, subtending visual angles of 4 × 5 degrees. They were exposed for 400 milliseconds with an interval of 2,000 milliseconds between onsets of two successive images. Six blocks of 40 stimuli were delivered for each task. The order of the stimuli within each block and the order of the blocks were randomized for each subject and for each task.

Subjects were engaged in two different consecutive target detection tasks. They were required to keep a mental count of the number of targets presented in each block. During the first task, called "attention to gender" (ATG), the subject made a gender classification by counting men or women alternatively in every other block. In the ATG task, the ERPs

to target stimuli (men or women) were not included in statistical analyses. During the second task, called "attention to emotion" (ATE), subjects were instructed to count faces expressing surprise. ERPs to surprised faces were not included in statistical analyses. Each block was composed by the same stimuli, but the number of targets was not strictly the same in each block (variation of one or two targets between the blocks).

Recording Signal Analysis

Continuous SEEG was amplified and recorded with a 64-channel EEG device (SynAmps; NeuroScan Labs, El Paso, TX). A bipolar electrooculogram was recorded from the supraorbital ridge and outer canthus of the right eye. The nose was used as the reference site, and the ground was located on the mediofrontal scalp (Fz site).

SEEG was recorded continuously with a 1,000Hz sampling rate through a bandpass of 0.1–200Hz. A 200-millisecond prestimulus baseline correction was performed. Epochs with eye blink artefacts greater than 100μV on electrooculogram and epileptic transient activities greater than 250μV were rejected. Mean ERPs to all face expressions were computed for both tasks and for each recording site in each patient. The averaging was conducted on an analysis time of 600 milliseconds with a sampling frequency of 1,000Hz.

Statistics

After visual inspection of the curves of averaged potentials in each patient, we observed differences between responses to disgust and to the other emotions. We visually defined a time window for each patient in which differences were maximal. For each patient, the mean amplitudes of single trial potentials to nontarget stimuli were calculated during this time window. Before statistical analysis, these single trial mean amplitudes were screened for homogeneity of variance. Because the data met the assumptions required for the analysis of variance, they were entered as dependant variable in an analysis of variance (ANOVA), the emotions being the factor. Post hoc paired comparisons between emotions were performed using Fisher's tests. For each patient, the precise bounds of the time window exhibiting a significant effect were determined using statistical analysis on single trial mean amplitudes over sequential 50-millisecond time windows shifted by steps of 25 milliseconds. To test the extending depth of the effect, we performed ANOVAs on the contiguous contacts, until reaching the absence of significance.

Cortical Stimulation Procedure

This procedure, as well as the recording of visual-evoked potentials, is part of the functional mapping of eloquent cortical areas performed routinely before epilepsy surgery in patients implanted with depth electrodes. Stimulation of cortical areas was applied using SEEG recording electrodes. Square pulses of constant polarity were applied between the two deepest contacts located in the insular cortex. Patients were fully informed of the cortical stimulation procedures

and gave their consent. See Ostrowsky and colleagues for details on the stimulation procedure.[15]

Results

TakPfuLb

ATTENTION TO GENDER TASK. The mean performance of the 13 patients was 98.1% correct (±2.4). The proportion of correct responses was 100% in Patient B.M., 91% in Patient M.B., 99% in Patient P.G., and 97.5% in Patient S.D..

ATTENTION TO EXPRESSION TASK. The mean performance of the 13 patients was 85.9% correct (±7). Only two patients (S.D. and another patient) had less than 80% correct responses. The proportion of correct responses was 100% in Patient B.M., 85% in Patient M.B., 90% in Patient P.G., and 77% in Patient S.D.. It was noticed that Patient S.D. was drowsy during this second task, that is, ATE task.

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Among the 17 contacts in the insula, three were lying in the short gyri (two in the right hemisphere [RH] and one in the left [LH]), six in the posterior part of the anterior long gyrus (four in RH, two in LH), four in the anterior part of the anterior long gyrus or its boundary with short gyri (three in RH, one in LH), and four in the posterior part of the posterior long gyrus (three in RH, one in LH; Fig 1).

IlarEtdelPial

VISUAL ANALYSIS. On visual inspection of traces of mean potentials in both tasks, 4 of the 17 insular contacts in four patients (M.B., B.M., P.G., and S.D.) showed amplitude differences between responses to disgust and to other facial expressions. These four contacts were located in the anterior part of the anterior long gyrus (see Fig 1). Figure 2 presents the averaged ERPs elicited by faces expressing fear, happiness, disgust, or no emotion (neutral faces) recorded in the insula of these four right-handed patients.

STATISTICAL ANALYSIS. Statistical analyses on single trial potential amplitudes were performed on all insular contacts in the 13 patients over the time window in which visual inspection showed a difference between expressions. ANOVAs performed on single trial potential amplitudes showed a significant effect of the factor "emotion" during the ATE task in three patients, and in two patients in the ATG task. Latency limits of significant differences were determined by the shifting window analysis described in Patients and Methods.

In the ATE task, the effect of the factor "emotion" appeared between 250 and 500 milliseconds after stimulus onset in Patient M.B., 325 and 450 milliseconds
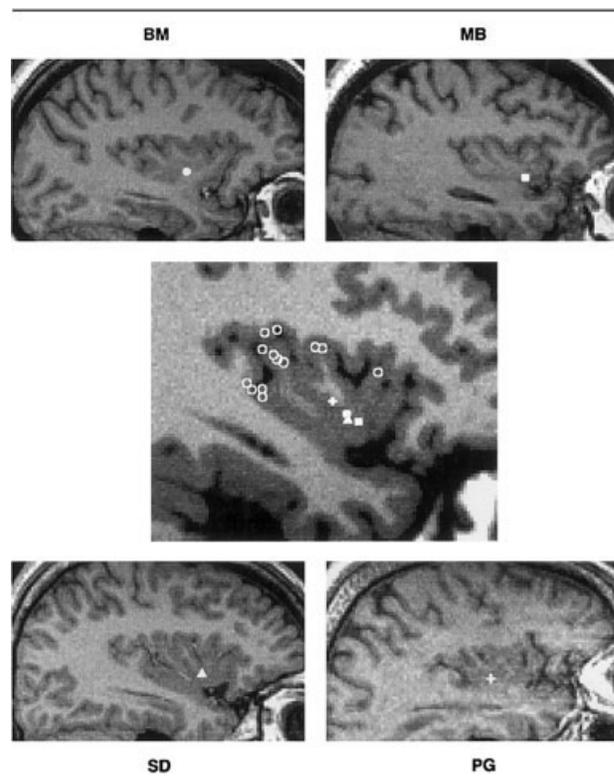

Fig 1. Th17 dastguildo fb13 pixefiloabplango nening thelbbyfixpiulia fbhg (PainB.M., M.B., S.D., and P.G.). Th beplodla fa lgoll luf (in bedbhg jelduisfabut hivohduflarg Tbasfbhfi pia bdfpavojl(M.B., squares; B.M., filled circles; P.G., plus signs; S.D., triangles), areal jpikeal prfbainh g Albdarut (open circles) ida daypbpoojl Nohtbaeal jpikedl la.

in Patient B.M., and between 300 and 500 milliseconds in Patient P.G. (Table). Post hoc paired Fisher's tests between emotions showed that responses to disgust were significantly different from all other emotions in these time windows for the three patients, and that there was no difference between the amplitudes related to the other emotions.

During the ATG task, ANOVA showed similar significant differences in two patients: between 350 and 600 milliseconds of latency in Patient M.B. and between 400 and 600 milliseconds in Patient S.D. (see Table). Post hoc Fisher's tests also showed a significant difference between disgust and all other emotions with no difference between the other emotions.

In these patients, the significant differences were limited to one or two adjacent contacts (see Table).

MB-I1- ATE

PG-I1-ATE

BM-I1-ATE

MB-I1-ATG

SD-I2-ATG

DISGUST
HAPPINESS
FEAR
NEUTRAL
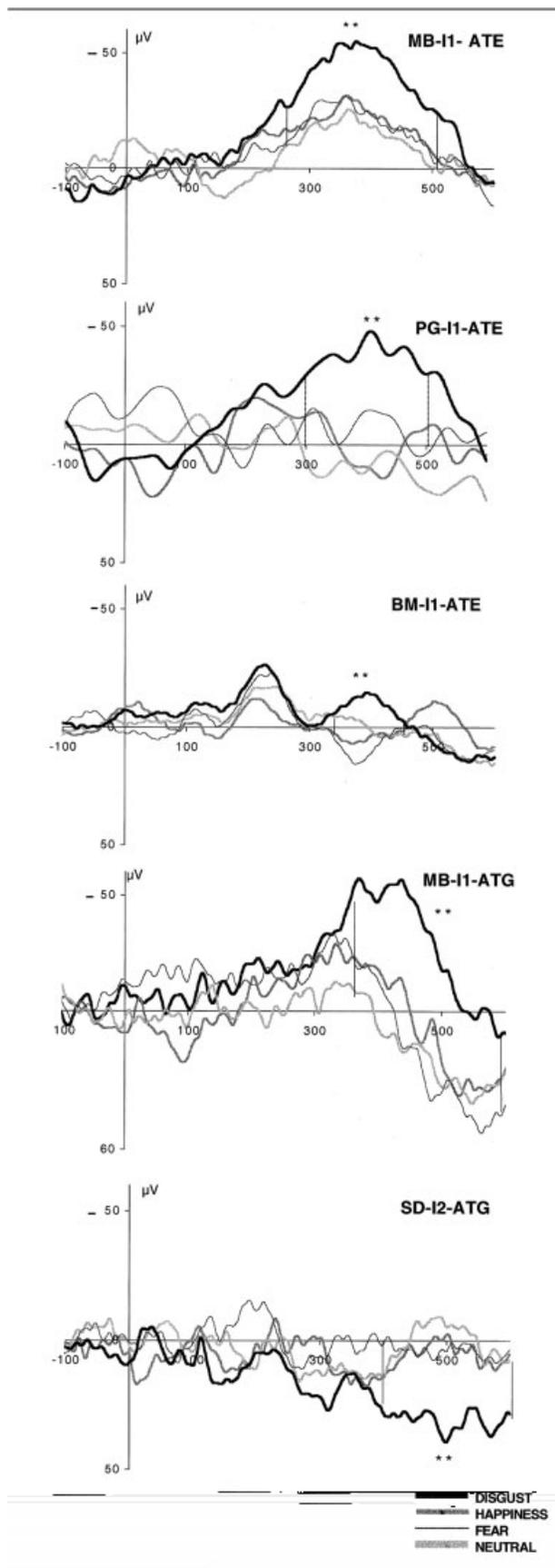
Event-related Potentials in Fusiform Gyrus and Calcarine Area

The four patients exhibiting a disgust effect in the insula also underwent implantation of electrodes in the fusiform gyrus where large potentials to faces were recorded. Single trial ERPs in fusiform gyri in the four patients and in right superior calcarine bank in Patient M.B. were analyzed to compare amplitudes and latencies between the two tasks. For each task, peak amplitudes and peak latencies were entered into ANOVAs with nontarget face expressions (neutral, fear, happiness, and disgust). ANOVA showed no difference among ERPs to facial expressions between the ATG and ATE tasks. These ERPs also were analyzed in each task during the time windows exhibiting a disgust effect in insula. The ANOVA did not show any significaent and

as an example, the potentials recorded in the fusiform gyrus and calcarine bank in Patient M.B. in the two tasks.

Insular Stimulations

Clinical responses to insular stimulations delivered through contacts recording ERPs to disgust were evoked in three of the four patients. Two of them (B.M. and P.G.) reported unpleasaent sensation in the throat spreading up to the mouth, lips, and nose. It was not painful but described as "s, to stand."
The third patient reported paresthesia in the contralateral hand when the deepest contact was stimulated. This contact was not lying in the insula, but in the underlying white matter.

Discussion

This study exploring the processing of emotional faces in the insula points out significaents, ans between ERPs elicited by disgusted faces and by the other emotional faces between 300 and 600 milliseconds after

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Task (Patient)	Insular Contact Names		
	I1	I2	I3
ATE			
M.B.	Tal (35; 7; −9) 250–500msec ANOVA $p = 0.006$ D/H $p = 0.01$ D/N $p = 0.001$ D/F $p = 0.005$	Tal (39; 7; −9) 250–500msec ANOVA $p = 0.07$ NS	Tal (42; 7; −9) 250–500msec ANOVA $p = 0.1$ NS
B.M.	Tal (−32; 2; −4) 325–450msec ANOVA $p = 0.02$ D/H $p = 0.01$ D/N $p = 0.02$ D/F $p = 0.003$	Tal (−36; 2; −4) 325–450msec ANOVA $p = 0.06$ NS	Tal (−39; 2; −4) 325–450msec ANOVA $p = 0.1$ NS
P.G.	Tal (35; −6; −3) 300–500msec ANOVA $p = 0.004$ D/H $p = 0.003$ D/N $p = 0.02$ D/F $p = 0.001$	Tal (38; −6; −2) 300–500msec ANOVA $p = 0.003$ D/H $p = 0.004$ D/N $p = 0.009$ D/F $p = 0.0008$	Tal (41; −6; −2) 300–500msec ANOVA $p = 0.09$ NS
ATG			
M.B.	Tal (35; 7; −9) 350–600msec ANOVA $p = 0.002$ D/H $p = 0.004$ D/N $p = 0.0005$ D/F $p = 0.004$	Tal (39; 7; −9) 350–600msec ANOVA $p = 0.03$ D/H NS D/N $p = 0.03$ D/F $p = 0.007$	Tal (42; 7; −9) 350–600msec ANOVA $p = 0.7$ NS
S.D.	Tal (41; 7; −6) 400–600msec ANOVA $p = 0.4$ NS	Tal (45; 7; −6) 400–600msec ANOVA $p = 0.006$ D/H $p = 0.005$ D/N $p = 0.001$ D/F $p = 0.01$	Tal (48; 7; −6) 400–600msec ANOVA $p = 0.2$ NS

ANOVAs of mean amplitudes of elementary event-related potentials (ERPs) to facial expressions in the specified time windows for the two tasks, that is, attention to expression (ATE) and attention to gender (ATG), for the four patients (M.B., B.M., P.G., and S.D.). ANOVAs were performed on responses recorded on electrode contacts lying in the Insula, I1 designing the deepest contact. The Talairach coordinates of the contacts (in millimeters) are reported on the first line of each cell. Mean amplitudes of elementary potentials (48 before artifact elimination in the ATE task, 24 in the ATG task) were defined as dependant variable and the four different expressions as factor analysis (D = disgust; H = happiness; N = neutral; F = fear). When ANOVA showed an expression effect, post hoc Fischer's tests were performed between the different emotions (D/H, D/N, D/F, H/N, H/F, and N/F). They show that ERPs to disgust were different from each of the other emotional expressions. Note that these differences are focused on one or two contacts only.

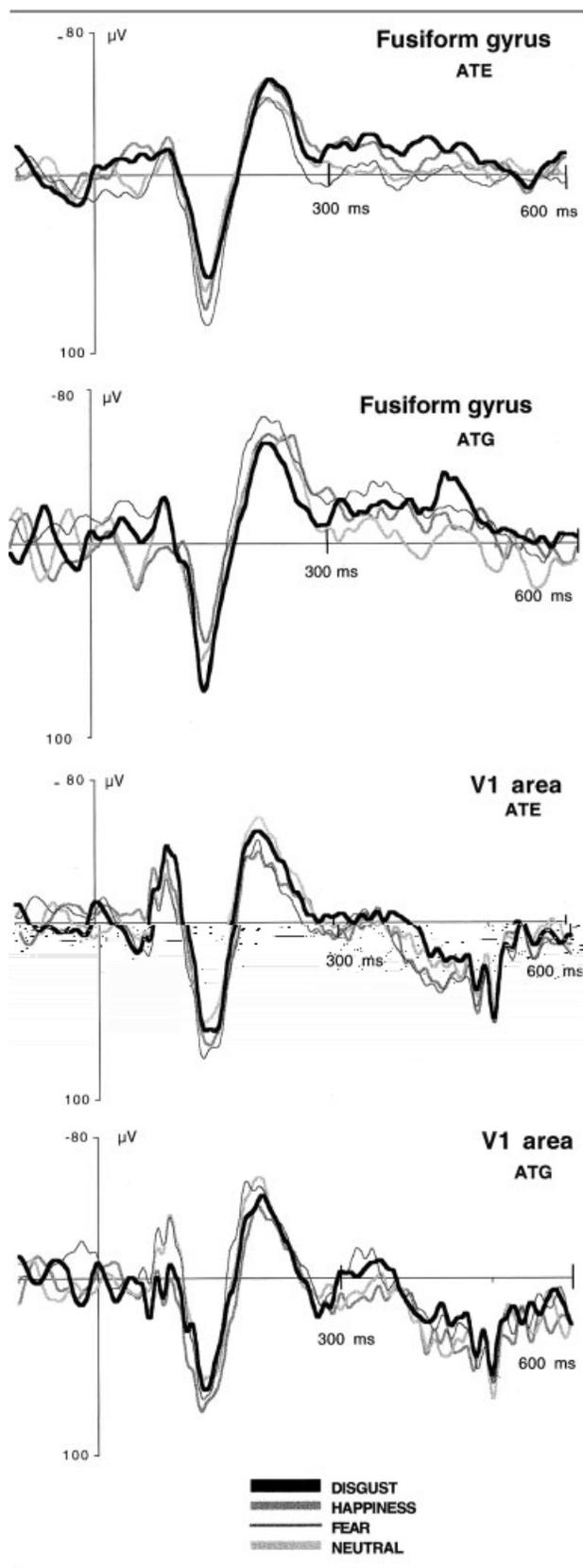Tal = Talairach coordinates; ANOVA = analysis of variance; NS = not significant.

stimulus onset. In what follows we will call this differential activity related to the disgust facial expression the "disgust effect."

What Does Disgust Effect Take Place?

The differences between ERPs related to disgust and the other expressions were observed in the ventral anterior part of the insula. All contacts exhibiting these differences were lying in the anterior long gyrus or in its boundary with short gyri and all contacts located in this part of the insula were found to record this difference, at least in one of the two tasks, whereas more dorsal insular contacts did not. The ventral anterior insula thus appears to be specifically involved in the processing of disgusted faces. In each patient, the effect was limited to one or two contacts in depth, excluding a contribution of distant structures by volume conduction. This emphasizes the reliability of the involvement of the ventral anterior part of the insula.

Using functional MRI (fMRI), Phillips and colleagues have shown that anterior insula is involved in the discrimination of facial disgust expression.[5] This specific activation was located in the dorsal anterior insula, superior and anterior to our recordings sites. The

Fusiform gyrus
ATE

Fusiform gyrus
ATG

V1 area
ATE

V1 area
ATG

■ DISGUST
▨ HAPPINESS
— FEAR
░ NEUTRAL

contact of our series lying in the dorsal anterior insula did not record specific responses to disgust (see Fig 1). This discrepancy may be related to a better spatial resolution of stereotactic intracranial recordings as compared with that of fMRI. However, the amount of explored sites in dorsal part of the anterior insula was limited in our study. Whereas the cytoarchitectonic map of insula has been extensively studied in monkeys, it remains poorly described in humans. Three cytoarchitectural fields of the macaque insula have been identified.[7] The ventral anterior agranular field surrounding the primary olfactory cortex is separated from the posterior-dorsal granular field by a transitional dysgranular field, with a gradual sequence of cytoarchitectonic changes. In our study, the insular contacts with specific responses to disgust are all lying in the ventral anterior part of insula. We localize these contacts in the agranular and/or dysgranular fields, known to be connected to areas involved in the discrimination of face features in monkeys, such as the superior temporal sulcus,[16,17] as well as olfactory, gustatory, and autonomic structures.[18,19] These connections may allow the discrimination of facial disgust expression.

The insular processing of disgust expression may represent one aspect of a wider "conceptual knowledge"[20] of the emotion "disgust" processed by a network involving the ventral anterior insula.[3] Interestingly, two patients reported quite unpleasant sensation in the throat and inferior face when the ventral anterior contacts were stimulated. Both ERPs and stimulation results suggest that this insular area plays a role in detection of disgust in congeners and feeling disgust oneself. Mechanisms used to perceive disgust in others thus would be linked to those involved in experiencing that emotion oneself, suggesting that observing might be a way to learn our emotional reactions.[21]

Note that we do not have yet enough data to compare properties of right versus left insula.

When Does Disgust Effect Take Place?

The specific responses to disgust were observed between 250 and 600 milliseconds after stimulus onset. This effect occurs later than the classic potentials related to faces recorded from ventral occipitotemporal cortex peaking around 170 milliseconds.[22] It also appears later than activities related to facial expression discrimination in the right superior temporal cortex re-

Fig 3. Examples in V1 area and in fusiform gyrus in Patient M.B. obtained in (ATE) and (ATG) ... No ... plus ... ERPs of ... in ... 300 ... 600 ...

corded between 140 and 250 milliseconds by magnetoencephalography.[23] Thus, the specific responses to disgusted faces in the ventral anterior insula occur later than activities related to the extraction of perceptual information in occipital and temporal neocortices. Moreover, potentials to disgust in insula peak later than potentials related to fearful faces recognition in human amygdala, which peak between 150 and 180 milliseconds.[24] That may be linked to a minor role of disgust recognition in survival behavior compared with that of fear recognition, which may be processed faster by subcortical structures.[25]

Our results were obtained in the context of patients with partial epileptic seizures, but the data were recorded from sites not considered as epileptogenic in these particular patients. It does not exclude functional impairment of the whole temporal lobe, which could delay latencies of insular responses.

Is There an Effect of Selective Attention to Facial Emotion upon Responses to Disgust

fMRI studies have shown that the activity in several brain structures, that is, amygdala, insula, orbitofrontal cortex, and superior temporal sulcus, is modulated by specific attention to facial expressions.[26,27] The manipulation of spatial attention was found to modulate the fusiform responses to emotional faces, whereas it did not affect the responses of the amygdala to fearful faces.[28] Thus, spatial distribution and intensity of brain activities related to facial features such as emotional expression are modulated by attention.

In our study, we were expecting an influence of specific attention to facial expression on responses recorded in the insula. The ATE task can be considered as an explicit emotion judgment task whereas, in the ATG task, the facial emotion might be implicitly processed. The specific responses to disgust started at approximately 300 milliseconds and lasted 200 milliseconds in the ATE task. They started 100 milliseconds later, lasting also 200 milliseconds, in the ATG task. Moreover, the disgust effect was observed more often in the explicit ATE task than in the ATG task. Thus, the specific attention to facial expressions favored the occurrence of the disgust effect in the ventral anterior insula and shortened its latency. Could it be interpreted as an arousal effect related to the complexity of the task? Neither latency nor amplitude differences among potentials to facial expressions in the explicit ATE versus implicit ATG tasks were observed in occipital cortex and fusiform gyrus (see Fig 3). That rules out a general nonspecific arousal effect. Thus, there is a selective attention modulation on disgust expression processing in the ventral anterior insula, prominent between 300 and 500 milliseconds of latency. This positive modulation by explicit emotion recognition seems to be opposite to the specific attention modulation on

amygdala fear-related activity, which decreases with explicit emotion categorization as compared with implicit recognition.[29,30] In our study, the type of attention modulation and the late latency recorded activities to disgust suggest that ventral anterior insula is involved in a sustained disgust evaluation required in a categorization task as opposed to a more dynamic process of fear in the amygdala.

In conclusion, intracranial electrophysiological recordings combining exceptional temporal and spatial resolution appear to be quite an appropriate method to explore human deep cerebral structures. It is the first time to our knowledge that ERPs to a specific facial expression, that is, disgust, could be directly recorded in insula in humans. These results show that the ventral anterior fields of the human insula are specifically involved in the processing of this emotional expression, and that this processing is sensitive to specific attention to facial expression. Temporal analysis shows that insula ERPs to disgust occur later than evoked responses in visual striate and extrastriate areas. These results suggest a crucial role of the ventral anterior insula in the processing of facial emotional expression, which represents only one aspect of a global emotion processing.

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